REMARKS

This amendment is in response to the Non-Final Office Action dated January 11, 2007. By said Office Action, claims 5-14 were rejected under 35 USC § 103(a), as being unpatentable over Altman et al. (Proc. Nat. Acad. Sci. USA; 1993, 90: 10330-10334) in view of Matsumura et al. [J. Biol. Chem.; 1992, 267 (33): 23589-23595].

Claims 1-14 are in this case. Claims 1-4 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 5-14 have been rejected. New claims 15-20 have been added.

35 U.S.C. § 103(a) Rejections - Altman in view of Matsumura

The Examiner has rejected claims 5-14 under 35 U.S.C. § 103(a) as being unpatentable over Altman et al. in view of Matsumura et al. The Examiner states that Altman teaches the production of soluble MHC class II complexes in E. coli; the purification of MHC class II from inclusion bodies; the in vitro refolding of the MHC molecules; the association of the MHC molecules with antigenic peptides and that no other proteins are required for the efficient folding of the MHC molecules and that carbohydrate modification is not necessary for T cell recognition; that production in E. coli provides large quantities of MHC molecules needed for conformational and functional studies and that production of empty MHC class I molecules is possible but is inhibited by the instability of the complex at physiological temperatures. The Examiner further states that Altman does not teach the production of MHC class I molecules. In addition, the Examiner states that Matsumura teaches the production of soluble empty MHC class I molecules in Drosophila cells and the binding of peptides to the complexes and that it would have obvious to a person having ordinary skill in the art to use the method of Altman to produce the MHC class I molecules of Matsumura in E. coli, and that one would have been motivated by the teachings of Matsumura that empty MHC class I molecules are stable at lower temperatures and can be loaded with antigenic peptides. In addition, the Examiner states that while Altman teaches that the EMPTY MHC class II molecules are not stable at physiological temperatures Altman is silent regarding whether the complexes comprising the MHC class II molecules and antigenic peptides are thermally stable at

a temperature of 60 °C, and that silence about a particular property does not necessarily constitute its absence. The Examiner further states that there does not appear to be any material differences between the instantly disclosed MHC class II/antigenic complexes that would confer any special properties upon them that would not be present in the complexes of the prior art. The Examiner's statements are respectfully traversed.

Applicant respectfully urges that a *prima facie* case of obviousness has not been properly set forth. There is no reasonable expectation that the method of generating the MHC class I-peptide complexes based on the teachings of Altman and Matsumurra would result in the thermally stable complexes of the present invention.

Altman teaches that MHC class II-peptide complexes are unstable at physiological conditions and not only empty MHC class II molecules as stated by the Examiner. Thus, Figure 1B in Altman et al. depicts the *in vitro* folding yields of MHC class II-peptide complexes [*i.e.*, the Ec-I-Ek (MHC class II molecule) in the presence of the bioMCC antigenic peptide] [see the title of the Y axis of Figure 1B, Page 10331 in Altman et al., as well as the description of the results of Figure 1B on Page 10332, right column, second paragraph, lines 4-22 (note in particular line 5 for the recitation "Ec-I-Ek-peptide complex")]. The "bioMCC peptide" and its use for preparing the MHC class II-peptide complex are described on Page 10331, left column, lines 2-4 and lines 25-26 in Altman et al.. Thus, as stated by Altman et al., the in vitro folding yields of the bioMCC•Ec-I-E(k) (*i.e.*, the MHC class II-peptide complex) presented in Figure 1B are comparable at 15 °C and 25°C but are decreased at a temperature of 37°C (lines 14-17, right column, Page 10332 in Altman et al.). In fact, based on these results the subsequent folding reactions were carried out at 25°C (Page 10332, right column, lines 20-21 in Altman et al). Altogether, these results demonstrate the limited thermal stability of the MHC class II-peptide complexes produced by Altman et al., which are completely unstable at a temperature of 37°C, let alone at a temperature of 60°C. Thus, it is Applicant's position that the art of Altman is not silent regarding the stability of complexes comprising the MHC class II molecules and antigenic peptides and in fact Altman clearly shows that such complexes are unstable at high temperatures.

Similarly, the MHC class I-peptide complexes generated in Drosophila cells by Matsumurra were stable at 23°C, and gradually lost their thermal stability when the temperature was increased to 37 °C (note the faint bands in lanes 6 and 8 from the left in Figures 1D, Page 23951 in Matsumura et al., resulting from the instable MHC class I-peptide complex formed in the presence of the VSV-7 or VSV-9 peptides). In addition, at a temperature of 47 °C both MHC class I-peptide complexes formed in the presence of the VSV-7 peptide (the 10th lane from the left in Figure 1D) and VSV-9 peptide (the 12th lane from the left in Figure 1D) lost their stability (i.e., were completely unstable), while the stability of the MHC class I-peptide complex formed in the presence of the VSV-8 peptide was significantly decreased (note the faint band on the 11th lane from the left in Figure1D). Thus, these results clearly show that the MHC class I-peptide complexes generated according to Matsumura et al., lose their thermal stability at temperatures higher than 37 or 47 °C, let alone at higher temperatures such as 60 °C. Extrapolation of the intensity results shown in Matsumura et al., which was performed by the present inventor (shown in an Appendix and declaration), predict a complete breakdown of the MHC class I-peptide complex of Matsumura et al., at a temperature of 50 °C.

Thus, it is Applicant's position that the Examiner failed to establish a *prima facie* case of obviousness by combining the teachings of Altman and/or Matsumura in order to obtain the thermally stable complexes produced by the claimed methodology.

Support for new claims 15-19 can be found on Pages 46 (lines 10-15) and 67 (lines 4-7) of the instant application. Support for the limitation "upstream" in new claim 20, can be found, for example, on Page 7 (lines 2-6), Page 8 (lines 14-19), Page 22 (from line 17) – Page 23 (line 2) of the instant application.

Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Enclosures:

Petition for extension of time (2 months)
Additional claims transmittal
Appendix
Signed declaration
CV

In re Application of: YORAM REITER
Serial No.: 10/075,257
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Examiner: Vandervegt, Francois P
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Appendix

The intensity of the bands shown in Fig. 1D of Matsumura M., et al., (JBC, Vol. 267, Page 23589-23595), which represent the MHC class I-peptide complexes formed in the presence of the VSV-7, VSV-8 or VSV-9 peptides was measured using a densitometer, averaged and plotted as a function of the temperature. Extrapolation of the linear line was used to predict the intensity of the MHC class I-peptide complexes at higher temperatures. Note the significant decrease in MHC class I-peptide complex intensity when the temperature was raised from 23°C to 37°C or 47°C and the predicted complete dissociation of the complexes (0 intensity) at a temperature of 55°C. These data conclusively show that the MHC class I-peptide complexes of Matsumura et al., are completely unstable at a temperature of 60°C.